term ''shaken baby syndrome''. In any other age group an unexplained encephalopathy and haemorrhage into the subarachnoid and subdural spaces would be labelled ''head injury'' and the same features with long bone and rib fractures would be labelled ''multiple injury''. In these circumstances it is the responsibility of the authorities, not the doctors, to investigate how the injuries occurred, and the separation of the therapeutic and investigative aspects of the condition may be advantageous to all. However, doctors must continue to do their duty to report suspected abuse and to perform carefully documented medical investigation in cases of suspected child abuse.

Arch Dis Child 2006;**91**:205–206.
doi: 10.1136/adc.2005.090761

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Epilepsy
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Preventing misdiagnosis of epilepsy

C D Ferrie

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Commentary on the papers by Hindley *et al* (see page 214) and Uldall *et al* (see page 219)

It has become axiomatic that the rate of misdiagnosis of epilepsy is high. A population based study mainly in adults found a misdiagnosis rate of 23%,[1] while 26% of subjects referred to a single adult neurologist with ''refractory epilepsy'' were found not to have epilepsy.[2] Hitherto, hard data in children on this has been lacking. Two studies in this month's *Archives* address aspects of this from different perspectives. Hindley *et al* report an eight year prospective study of the diagnoses made in children referred to a secondary level ''fits, faints, and funny turns'' clinic in Bury, UK.[3] Uldall *et al* report a retrospective study of the final diagnosis compared to the referral diagnosis of 223 children admitted during 1997 to the Danish Epilepsy Centre which takes referrals from the whole of Denmark.[4]

Hindley *et al* found that epilepsy was the diagnosis in only 23% of the children referred.[3] The largest diagnostic group was syncope of various sorts (42%). Other relatively common diagnoses were psychological non-epileptic events (8%), daydreaming (5%), night terrors (4%), migraine (3%), benign paroxysmal vertigo (2%), ritualistic movements, including gratification (2%), and parental anxiety/fabricated illness (2%). A miscellany of other conditions, including paroxysmal movement disorders, accounted for 8% of diagnoses. Fourteen per cent of patients remained undiagnosed. Unfortunately, the paper does not give referral diagnoses. It would be disingenuous to suggest that epilepsy was the preferred (or even likely) referral diagnosis in all. However, it is probable that it was suspected in many of those subsequently found not to have epilepsy.

Uldall *et al* found that 39% of those referred to the Danish Epilepsy Centre did not have epilepsy.[4] In 17% of referrals the reason for referral included concern that the diagnosis might not be epilepsy. However, even in those in whom the diagnosis of epilepsy was not in doubt at the time of referral, 30% were subsequently ''undiagnosed''.

Neither study was population based. The ''fits, faints, and funny turns'' clinic was not the only referral centre in Bury and the children studied included those already diagnosed elsewhere but referred for ongoing management. The Danish Epilepsy Centre is a tertiary referral centre. Nevertheless, there are two powerful messages from these studies: Firstly, in children with paroxysmal disorders, epilepsy is a minority diagnosis. Secondly, a significant minority of children diagnosed with epilepsy that have ongoing seizures, do not have epilepsy.

THE WIDER CONTEXT

Misdiagnosis of epilepsy in children has became an important issue politically and in the media in the UK following concerns raised about the practice of Dr Andrew Holton at the University Hospitals of Leicester NHS Trust.[5] The investigation of this conducted on behalf of the Trust's management by the British Paediatric Neurology Association (BPNA) concluded that 31.8% of subjects diagnosed with epilepsy had been misdiagnosed. The resulting legal action is likely to cost over £10 million.[6] Has Dr Holton been vindicated, given that his misdiagnosis rate is similar to that reported by Uldall et al? Probably not. The population treated by Dr Holton is likely to have been very different from that of the Danish Epilepsy Centre. Dr Holton's practice probably contained many more children requiring secondary rather than tertiary level epilepsy services. Moreover, concerns were also raised about Dr Holton's treatment of epilepsy.

Concerns regarding the standard of care afforded to children diagnosed with epilepsy in the UK were also raised by the National Sentinel Audit of Epilepsy Related Death.[7] This investigated 22 epilepsy related deaths in children and found inadequacies in the care they had received in 77%. Fifty nine per cent of the deaths were considered to have been possibly or potentially avoidable.

Misdiagnosis of epilepsy is important for three main reasons. Firstly, simply having a diagnosis of epilepsy can be detrimental. Restrictions on leisure activities, however unjustified they usually are, are still commonly applied. Educational expectations are often lowered and employment prospects may be blighted. This is bad enough if you have epilepsy, but it is an even greater tragedy if you don't. Secondly, as reported by Uldall et al, many subjects who are misdiagnosed are treated with antiepileptic drugs.[4] While series adverse effects of antiepileptic drugs are rare, minor adverse effects are common. Thirdly, the subject is denied a correct diagnosis. Treatable conditions, such as events due to psychological disturbances, are missed; occasionally, as with prolonged QT syndromes causing cardiac syncope or hyperekplexia causing tonic non-epileptic seizures, these may be life threatening. More commonly, the patient will have a benign condition for which no treatment, other than reassurance, is needed.

REASONS FOR MISDIAGNOSIS
The main reasons why misdiagnosis of epilepsy is common are:

- There is a false tendency to think of epilepsy as a single disorder
- The diagnosis is mainly based on the history and there is usually no confirmatory test
- The EEG is abused
- There is a large differential diagnosis
- Many clinicians charged with diagnosing paroxysmal disorders do not have sufficient knowledge of the clinical features of epileptic and non-epileptic seizure disorders
- There is a false perception that to miss a diagnosis of epilepsy carries grave risks
- Most clinicians with responsibility for diagnosing epilepsy do not have easy access to the full range of appropriate investigations.

Epilepsy is not a single disorder
It is often stated that epilepsy is the commonest ''serious'' neurological condition. This is an illusion, sometimes convenient when arguing for funds. The term refers to a large and diverse group of disorders (probably hundreds) which share the tendency to have recurrent epileptic seizures. Collectively, these may be quite common but individually most are rare or very rare. The clinician who is content to simply make a diagnosis of ''epilepsy'' is likely to over-diagnose it. The discipline of always attempting syndromic diagnosis highlights those patients whose features do not really fit with any epilepsy and in whom non-epileptic seizures are likely.

Hindley et al were able to ascribe a specific syndrome diagnosis in 48% of cases. In only 9% was a diagnosis of unclassified epilepsy given.[3]

Epilepsy is diagnosed on the history without any confirmatory tests
The epilepsies are almost unique among the more common medical disorders (not withstanding the comments above) in that their diagnosis is usually made entirely on the basis of the history. The good diagnostician is not someone with hard to obtain technical skills, but rather a clinician who has the time to take a full history, the patience to track down often difficult to locate eyewitnesses, the communication skills which encourage children and adults to recount events accurately, and the medical knowledge of often rare and esoteric conditions which may be only encountered once or twice in their professional career. Unfortunately, epileptic seizures often occur in inconvenient places for observation and involve a complex series of events occurring both sequentially and concurrently. Even if a first-hand account can be obtained it is asking a lot of eyewitnesses to give an accurate account of such events, particularly as they are likely to have been very frightened at the time. Sensory seizures may include experiential symptoms without normal counterpart. Hence, even if the child has reasonable language skills, there may not be any descriptive words to describe their ictal experiences. Other sensory seizures involve distortions of time, and amnesia is common after many seizures.

In most areas of medicine today, the diagnosis made on the history is only the prelude to performing definitive diagnostic tests. Unfortunately, there is no test for epilepsy, although many clinicians think there is—the EEG. The EEG lacks both the sensitivity and the specificity required to make it useful in the initial diagnosis.[8] Only about 40–50% of children with definite epilepsy have epileptiform abnormalities on a single interictal EEG recording, and up to 3.5% of children who do not have epileptic seizures have epileptiform abnormalities on interictal EEG.

The EEG is abused
Over-interpretation is an important cause of misdiagnosis of epilepsy.[9] Developmental changes in the normal EEG, background EEG abnormalities, and ''non-epileptogenic epileptiform'' abnormalities have all been used to erroneously support the diagnosis of epilepsy. The standard of EEG reporting is very variable. Paediatric EEGs are reported by paediatric neurophysiologists, neurophysiologists, paediatric neurologists, adult neurologists, and psychiatrists. Neurophysiologists can qualify with minimal exposure to paediatric epilepsy. Paediatric neurology training in EEG may mainly consist of sitting beside someone else reporting EEGs, while the likely lack of knowledge possessed by adult neurologists and psychiatrists is frightening. Paediatricians can qualify without understanding the significance of the various features referred to in a well written EEG report.

The differential diagnosis of epilepsy in children is huge

Epileptic seizures are protean in their manifestations and for this reason there is a huge differential diagnosis. NICE guidelines give 36 differential diagnoses of epileptic seizures in children and the list could be added to.[10] Even to the epileptologist this is daunting. However, in most instances the conditions misdiagnosed as epilepsy are relatively common with characteristic features. In particular, in many of them attacks are characteristically provoked and/or there are initial or "warning" symptoms unlike those commonly encountered during epileptic seizures. Paying particular attention to these helps avoid misdiagnosis in many cases. Incomplete history taking was the principle reason for misdiagnosis identified by Smith and colleagues.[2]

Clinicians making the diagnosis may not be up to it

Most children are diagnosed by general and community paediatricians. Does their training equip them for this task? There is no requirement for a paediatrician in training to spend any time in paediatric neurology. By the time they qualify most will have only seen a few children with the more common epilepsy syndromes and will have never even heard of many of the rarer causes of non-epileptic seizures. Paediatricians are not now expected to deal with child abuse without extensive targeted training. It is doubtful if they would attempt to manage children with hypothyroidism, diabetes, or a ventricular septal defect without having received specific training either in the relevant specialty or else as part of a shared-care agreement with the relevant sub-specialist. Why is epilepsy different?

False perceptions about the risk of missing epilepsy

Previously, orthodox opinion was that "seizures beget seizures" and it was hoped that early treatment with antiepileptic drugs improved prognosis. Delaying treatment might increase the likelihood of "chronic epilepsy". Evidence does not support this view.[11] Any delay in starting treatment is likely to have no effect on the outcome. Indeed many of the commoner childhood epilepsies do not require regular antiepileptic drug treatment. It is possible, but not proved, that some rare childhood epilepsies (the epileptic encephalopathies) are an exception to this, but concern about these should not unduly influence the clinician.

Recent highlighting of the risk of epilepsy related deaths, including sudden unexpected death in epilepsy (SUDEP), may also put pressure on clinicians, fearful of the consequences of delaying treatment. However, while standardised mortality rates in subjects with epilepsy are increased, the increased risk to the individual is usually very small, particularly in children.[12]

Clinicians do not have access to appropriate investigative facilities

Finally, although the diagnosis of the epilepsies is usually principally made on the history, there are instances where investigations can be very helpful. A further reason for a high rate of misdiagnosis is the failure to use such investigations appropriately and/or difficulty accessing investigations. Video recording of the subject's attacks can be extremely helpful in making the correct diagnosis. A useful exercise is to ask a colleague to view a recording of an epileptic seizure and then ask them to describe it. The difficulties faced by lay eye-witnesses immediately become apparent. Many parents find it easy to make recordings of their child's "funny dos". Indeed, because many types of non-epileptic attacks have clear precipitants, or occur in particular circumstances, they are often easier to capture on home-video recordings than are epileptic seizures, which tend to occur much less predictably.

Investigators who pass judgement on the misdiagnoses of others have often made extensive use of video-EEG—an investigation which may not have been available to the clinician responsible for the original diagnosis. Ictal EEG recordings (whether obtained by ambulatory methods or by video-EEG telemetry) can be indispensable in making the correct diagnosis in some children with paroxysmal disorders. Currently many services have great difficulty accessing these and other "specialist investigations". Children with difficult to diagnose paroxysmal events should not need to go through a protracted process before "earning" such investigations. In some cases a video-EEG may be appropriate at the time of the first consultation. It may be the only investigation required.

SERVICE IMPLICATIONS

Radical changes to services are required if misdiagnosis of epilepsy is to be reduced. In the UK, NICE guideline provide a framework for this.[10] They state that the diagnosis of epilepsy in children should be made by a specialist, defined as "a paediatrician with training and expertise in the epilepsies". A consensus conference convened to inform the development of SIGN guidelines on epilepsy recommended that diagnosis should be confirmed by a consultant with expertise in epilepsy as shown by: training and continuing education in epilepsy; peer review of practice; and regular audit of diagnosis.[13] It also recommended that epilepsy should be a significant part of their clinical workload, equivalent to at least one session a week. Surely the days when all paediatricians should be expected to or should expect to manage children with epilepsy, out with the emergency situation, have ended.

Children with epilepsy should be managed in the context of a managed clinical network and according to an agreed care pathway. Named paediatricians should be responsible for managing secondary level services. Not all children with epilepsy or suspected epilepsy need to be seen by the named paediatrician, but all those diagnosing children should be confident that they fulfil the NICE criteria of a specialist.

In recognition of the training needs, the BPNA, encouraged by the RCPCH, has developed paediatric epilepsy training courses (PET). These are at three levels. Level 1 is designed to meet the needs of: paediatricians who do not have responsibility for providing secondary level epilepsy services; general practitioners; some epilepsy nurses; and those with responsibility for children with epilepsy in education and social services. PET 2 is designed for paediatricians with responsibility for secondary level epilepsy services. PET 3 is designed for those providing tertiary level epilepsy services. Further details are available on the website of the BPNA (www.bpna.org.uk).

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Screening

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Newborn screening for cystic fibrosis: do we need a second IRT?

J F Price

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Commentary on the paper by Massie *et al* (see page 222)

Newborn screening for cystic fibrosis (CF) has been possible since 1978, but national screening programmes have proved highly contentious and as yet have only been adopted in a minority of European countries and North American states. The main issue has been whether early diagnosis through screening results in long term clinical advantage, particularly in lung function. Recently the balance of benefit against harm has tipped in favour of screening,[1] providing that early diagnosis is followed by high quality care in specialised centres.[2] Screening programmes have been introduced in Northern Ireland, Wales, and Scotland. Only about 20% of babies are screened for CF in England, but a national screening programme is due to be implemented over the next three years. A good screening programme should identify the maximum number of cases that are likely to be severely affected, ensure that as many as possible of the missed cases are mildly affected, detect as few unaffected carriers as possible, allow for ethic diversity, and generate a minimum of anxiety. Three options are available; IRT-IRT, IRT-DNA, and IRT-DNA-IRT.

IRT-IRT involves measurement of immunoreactive trypsinogen (IRT) during the first week on the Guthrie blood spot and repeating the measurement at 3–4 weeks in those with initial high levels. This protocol for screening was introduced in East Anglia in 1979. The sensitivity of a raised 3–5 day IRT is high, but the positive predictive value is low. Because blood levels of IRT decay slowly in CF infants, a second IRT at 3–4 weeks increases the specificity, but about 1 in 200 newborn infants progress to the second blood test. This generates a period of anxiety in a large number of families who will turn out to have unaffected children.

IRT-DNA employs DNA analysis instead of a second IRT at 3–4 weeks. Infants with very high IRT in the first week undergo DNA analysis and those with at least one mutation have a sweat test. The advantage of IRT-DNA is that both tests can be done on the initial blood spot sample. New South Wales was one of the first regions to adopt an IRT-DNA screening programme, setting the cut-off for the first IRT at >99th centile and testing for the most common mutation, ΔF508. In this issue, Massie *et al* describe their experience of IRT-DNA screening in New South Wales between 1991 and 2003 and make the case against the measurement of a second IRT in babies with a high first IRT but no ΔF508 mutation.[3] During this time the screening programme identified 209 children with CF. Eighteen cases were missed, of whom seven were identified in the newborn period in other ways (meconium ileus or siblings with CF). The positive predictive value for an elevated IRT and one ΔF508 mutation was 1:8 (eight sweat tests were required to detect one case). However the yield for detecting additional cases by a second IRT in children who had a high first IRT but no ΔF508 mutation was extremely low. A second IRT was needed in about 400 infants to detect one more child with CF. To detect one "unexpected case" that was missed by ΔF508 screening and not diagnosed in the newborn period by other routes, a second IRT was required in nearly 700 infants.

IRT-DNA screening was commenced in Wales in 1996. At first DNA analysis was done on four common mutations (ΔF508, G551D, G542X, R553X), plus one with a high local frequency in Wales (1898+1G>A), but since 1999 a panel of 31 mutations has been used. By testing for more than one mutation the false negative rate was reduced to 3% and just six sweat tests were needed to detect one case.[4] The merits of this need to be weighed against the additional complexity and cost of the multiple DNA test, the detection of more carriers, and the identification of "mild" genotypes. Although the Welsh experience indicates that carrier identification is not perceived to be a problem,[5] the counselling incurs additional cost and the impact of disclosure of a carrier state on the child growing up has not been assessed.

The first two stages of the IRT-DNA-IRT protocol are the same as for IRT-DNA and sweat tests are done on babies with two detected mutations. However, a second IRT is measured at 3–4 weeks in babies with one mutation and a first IRT elevated above the 99.5th centile and in babies with no mutation but a first IRT extremely elevated above the 99.9th centile. Confirmatory sweat tests are done on those with an elevated second IRT. An IRT-DNA-IRT protocol with DNA analysis for 31 mutations has been used in Scotland since 2002 and will be adopted throughout England over the next three years. A refinement built into the new protocol for England will be a two stage DNA analysis. The four most common mutations will be tested first and a further 27 mutations will be analysed only in those with one common mutation. The purpose of this is to reduce the detection of carriers with mild mutations.

Applying existing UK data to the IRT-DNA-IRT protocol, it has been estimated that for those with one mutation a second IRT will be required in about 11 infants to detect one with CF, and in those with no mutations a second IRT will be needed in about 30 infants to detect one additional case. The critical assumption for those with no mutations is that a cut-off at 99.9% rather than 99% for the first IRT will give a better yield for the second IRT. The New South Wales experience does not entirely contradict this assumption. Their data show that the positive predictive value for a second IRT is 1:397 when the cut-off for the first IRT is set at 99%, but this improves to 1:59 if the cut-off is raised to 99.9%. Eight of their 11 "unexpected undiagnosed" cases had an initial IRT >99.9%. Another factor that may enhance the value of a second IRT in a